REMARKS

Information Disclosure Statement:

Five references cited on PTO-1449 submitted on September 25, 2001, were not considered as allegedly having improper citations. Applicants have submitted herewith the Third Information Disclosure Statement which includes four references with proper citations. Applicants did not submit the fifth reference that represents a SciFinder abstract of WO 96/23807 which has been already considered by the Examiner. Consideration of the Third Information Disclosure Statement is requested.

Claims Status:

1. Claims 1-15 and 18-33 are currently pending in this application.
2. Claim 17 has been cancelled.
3. Claims 1-16, 18-27 and 30-33 have been amended.

Claim Amendments:

Applicants submit herewith amendments to the claims in a revised format which is permissible since January 31, 2003, and will be mandatory in July 2003 upon adopting a revision to 37 C.F.R. § 1.121. The revised format waives the current provisions of 37 C.F.R. § 1.121(a), (c) and (d) for amendments to the claims, specification, and drawings. See http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/revamdtprac.htm.

Applicants have amended Claims 1-16, 18-27 and 30-33 and cancelled Claim 17, all without prejudice for future prosecution. The cancellation of Claim 17 makes no admission regarding the patentability of this subject matter and should not be so construed.

Applicants have amended Claims 1-3, 5-8, 10, 16, 20-27 and 30-31 by re-writing them into the proper Markush-type format.

Applicants have further amended Claims 1 and 3 by deleting the parenthetical phrase "(DNA or RNA)" from the claim language.

Claim 1 has been corrected by substituting the recitation "a 3'-labelled nucleic acid" with the recitation "a nucleic acid."

Claims 1, 2, 3, 11and 32-33 have been amended to provide a proper antecedent basis for compound (I) in monophospate form.

Claim 9 has been amended to correct dependency upon Claim 8 instead of Claim 1.

Applicants have further amended Claims 4-5 and 18-21 to provide the proper antecedent basis by substituting the recitation "the enzyme" with the recitation "an enzyme."

Applicants have yet further amended Claims 4-5, 18 and 20 to clarify which enzyme is being referenced by adding the recitation "of said enzymatic incorporation" into the claim language.

Claim 16 has been rewritten to specify the steps involved in the claimed process and adding a step of intermediate purification. Support for this amendment can be found in the specification at page 11, lines 19-25, and in Examples 1-12.

Applicants have yet further amended Claims 19 and 21 to clarify which enzyme is being referenced by adding the recitation "of said technique of enzymatic polymerization" into the claim language.

Applicants have amended Claim 11 to provide the proper antecedent basis by substituting the recitation "the derivative" with "the nucleotide derivative" and deleting the recitation ", the modified morpholino-nucleotide or the chain terminator" from the claim language.

Claims 1, 3, 10, 12-15 and 30-31 have been amended by deleting the phrases "derived from" and "derivatives" from the claim language.

Applicants have amended Claim 32 to provide the proper antecedent basis by deleting the recitations "the derivative," and "or the chain terminator" from the claim language.

Applicants have amended Claim 33 to provide the proper antecedent basis by substituting the recitation "the chain terminator" with the recitation "said at least one of the chain terminators" and deleting the recitation "the derivative, the modified morpholino-nucleotide or" from the claim language.

Accordingly, no new matter was added by way of these amendments. The Examiner is hereby requested to enter these amendments.

Rejections under 35 U.S.C. §101

Claims 16-17 stand rejected under 35 U.S.C. § 101 as improper process claims. Claim 17 has been cancelled rendering this rejection moot. Claim 16 has been rewritten to set forth the steps involved in the claimed process. Accordingly, this rejection is overcome. Withdrawal of the rejection is requested.

Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1-33 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification as to enable one skilled in the art to which it pertains to make and/or use the invention. The Office Action asserts that the disclosure is not seen to be sufficient to enable the preparation and use of compounds of formula (I) wherein R^3 is generically described as a label (other than labels are derived from fluorescein), protein, enzyme, fatty acid, or peptide. The rejection is respectfully traversed for the reasons set forth below.

Under 35 U. S. C. § 112, all that is required is that the specification describe the invention in such terms as to enable a person skilled in the art to make and use the invention. Thus, the specification must teach one skilled in the art how to make and use compounds of formula (I) wherein R^3 is a label, protein, enzyme, fatty acid, or peptide. The test of enablement is whether one reasonably skilled in the art (1) could make and use the invention (2) from the disclosures in the patent coupled with information known in the art (3) without undue experimentation. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988); *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); M.P.E.P. § 2164.01.

The law clearly states that "a considerable amount of experimentation is permissible, if it is merely routine." *In re Wands,* 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Further, the fact that experimentation may be complex does not necessarily make it undue. *Massachusetts Institute of Technology v. A.B. Fortia,* 774 F.2d 1104 (Fed. Cir. 1985); *In re Wands,* 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). Thus, the test of enablement is not whether any experimentation is

necessary, but whether, if experimentation is necessary, is it undue. *In re Angstadt*, 537 F.2d 498 (CCPA 1976).

Based only on consideration of the specific examples of the present application and disregarding the remainder of the application and information known in the art, the Office has erroneously alleged that the specification does not provide sufficient guidance to teach one skilled in the art how to make and use compounds of formula (I) wherein R^3 is a label, protein, enzyme, fatty acid, or peptide.

In contrast to the Office's allegation, the specification provides considerable guidance to enable a skilled artisan to make and use compounds of formula (I) wherein R^3 is a label, protein, enzyme, fatty acid, or peptide as evidenced by the attached Dr. Molko's Declaration.

The present invention teaches the nucleotide derivatives of formula (I) in which the substituted morpholine, which replaces the conventional saccharide portion, further comprises:

1) a hydroxymethyl function close to the ring oxygen, esterified with a triphosphoric acid group. This portion of the molecule mimics the 4',5' portion of nucleotides and allows binding by the polymerase or the transcriptase to the growing DNA or RNA chain.

2) an amine function substituted with R^2, which can optionally allow the grafting of a chromophore or of a biologically active group and, especially, which prevents the attachment of another nucleotide (interruption of the polymerization). Specification, page 9, line 21 through page 10, line 7.

Compared with the derivatives conventionally used, for example, in the Sanger method,

such as those described in documents [1], [2] and [3], the compounds of the present invention may be synthesized in a single step directly from ribonucleoside triphosphates. Specification, page 10, lines 8-12.

The advantage of these compounds lies in the very wide choice of groups R^2 (substituents of the morpholine ring) which may be used and which allow this ring to be functionalized. Functions such as acids, amines, thiols or ethers may be added and will allow the grafting of varied chemical compounds, in particular of labels that are useful for identifying DNA or RNA fragments. Specification, page 10, lines 13-20.

According to the present invention, R^3 may be selected from a very large set of well-known in the art and commercially available nucleotide labeling molecules. These molecules may be selected, for example, from radioactive products, luminescent, electroluminescent and fluorescent products, molecules capable of coupling with other molecules, molecules allowing interaction of antigen-antibody type, and enzymatic labels including hydrolases, particularly, phosphatases, esterases, ureases and glycosidases, or oxidoreductases, particularly, peroxidases. Specification, page 10, lines 21-27 and Dr. Molko's Declaration, ¶ 6.

Preparation of the compounds of formula (I) of the present invention wherein R^3 is a group derived from a label, a protein, an enzyme, a fatty acid or a peptide is based on the well-known methods as evidenced by the cited references [4]-[8] at page 11, line 1 through page 12, line 9 of the specification. Dr. Molko's Declaration, ¶ 7.

As further supported by Dr. Molko's Declaration, the nature of R^3 is not essential for the purposes of the present invention, and R^3 may be selected from a very large set of well-known in

the art and commercially available nucleotide labeling molecules. Dr. Molko's Declaration, ¶ 13.

Based on the disclosure of the specification in combination with the cited references, one skilled in the art would have been able to make and use compounds of formula (I) wherein R^3 is a label, protein, enzyme, fatty acid, or peptide that is a matter of routine experimentation, as evidenced by Dr. Molko's Declaration.

In conclusion, based on the arguments presented above and the information contained in Dr. Molko's Declaration, there is ample support for the specification being enabling. Applicants assert that, using the guidance provided in the specification, one skilled in the art would be able to make and use compounds of formula (I) wherein R^3 is a label, protein, enzyme, fatty acid, or peptide as evidenced by Dr. Molko's Declaration. The specification is therefore fully enabling and can be readily practiced by one skilled in the art. Accordingly, Applicants respectfully request that the 35 U.S.C. § 112, First Paragraph, rejections be withdrawn.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1, 3-17, 19, 21, 23, 25, 27, 29-31 and 33 stand rejected under 35 U.S.C. § 112, Second Paragraph, for allegedly being indefinite.

Independent Claims 1 and 3 have been rejected as incorporating the parenthetical phrase "(DNA or RNA)." Applicants have amended Claims 1 and 3 by deleting the parenthetical phrase "(DNA or RNA)" from the claim language. Accordingly, this rejection is overcome. Withdrawal of the rejection is requested.

Claims 1, 3, 10, 12-17 and 30-31 have been rejected as incorporating the phrases "derived from" and "derivatives." Applicants disagree with the Office's assertion that the phrases "fluorescein derivatives," "biotin derivatives" and "rhodamine derivatives" are indefinite because these terms are commonly used in the art. However, solely for the purposes of expediting the prosecution of the present application, Applicants have amended Claims 1, 3, 10, 12-16 and 30-31 by deleting the phrases "derived from" and "derivatives" from the claim language. Accordingly, this rejection is overcome. Withdrawal of the rejection is requested.

Applicants disagree with the Office's assertion that the term "sequencing" renders Claim 3, which is erroneously stated in the Office Action as Claim 5, and all subsequent dependent claims indefinite. This term, as used in Claim 3, is very clear for one skilled in the art for the following reasons. First, the definition of this term is available in any dictionary as evidenced by the attached pages from Oxford Dictionary of Biochemistry and Molecular Biology. Second, the reference to Sanger's method in the part "prior art" of the specification is enough to avoid any doubt concerning the meaning of this term in the specification. Accordingly, withdrawal of this rejection is respectfully requested.

Claims 4-5, 19 and 21 have been rejected as being unclear which "enzyme" is being referenced. Applicants have amended Claims 4-5 and 18-21 to provide the proper antecedent basis by substituting the recitation "the enzyme" with the recitation "an enzyme." Applicants have further amended Claims 4-5, 18 and 20 to clarify which "enzyme" is being referenced by adding the recitation "of said enzymatic incorporation" into the claim language. Applicants have further amended Claims 19 and 21 to clarify which "enzyme" is being

referenced by adding the recitation "of said technique of enzymatic polymerization" into the claim language. Accordingly, this rejection is overcome. Withdrawal of the rejection is requested.

Claims 16-17 have been rejected as improper process claims. Claim 17 has been cancelled rendering this rejection moot. Claim 16 has been rewritten to set forth the steps involved in the claimed process. Accordingly, this rejection is overcome. Withdrawal of the rejection is requested.

Claims, which are directly or ultimately dependent upon the amended claims, also incorporate their limitations and thus satisfy the requirements of 35 U.S.C. § 112, Second Paragraph for the reasons set forth herein above. Accordingly, Applicants respectfully request that the 35 U.S.C. § 112, Second Paragraph, rejections be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Claims 1-16

Claims 1-16 stand rejected under 35 U.S.C. § 103(a) as unpatentable over the combination of Torrence et al. U.S. Patent 4,515,781 (Torrence), Iversen U.S. Patent 6,365,577 (Iversen) and Meyer, Jr. et al. U.S. Patent 5,849,482 (Meyer). This rejection is respectfully traversed for the following reasons.

The present claims are directed to a morpholino-nucleotide of formula (I), a process for manufacturing a morpholino-nucleotide of formula (I) and uses of a morpholino-

nucleotide of formula (I). Thus, to establish a prima facie case of obviousness, the Examiner must show:

(1) some suggestion or motivation for one of ordinary skill in the art to modify or combine reference teachings in order to use a morpholino-nucleotide of formula (I) either in process for manufacturing a 3'-labelled nucleic acid fragment, which process comprises the enzymatic incorporation of a nucleotide derivative having as precursor a compound of formula (I) (Claim 1); or in process for modifying a nucleic acid fragment by enzymatic incorporation at the 3' end of a modified morpholino nucleotide having as precursor a compound corresponding to the formula (I) (Claim 2); or in process for sequencing a nucleic acid by the technique of enzymatic polymerization of the sequence complementary to this nucleic acid using chain terminators, in which at least one of the chain terminators has as precursor a compound corresponding to the formula (I) (Claim 3) or obtain the structures of morpholino-nucleotides of Claims 12-15 using the process of Claim 16; and

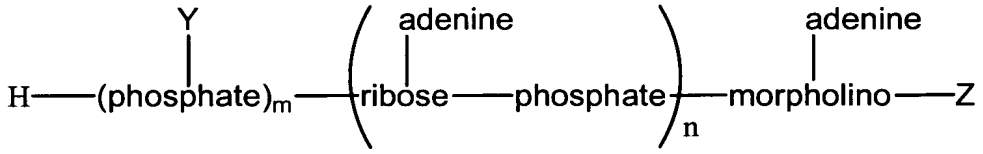
(2) a reasonable expectation of success of such uses of a morpholino-nucleotide of formula (I), structures or process.

The teaching or suggestion for the claimed uses of a morpholino-nucleotide of formula (I) and structures and the reasonable expectation of success must both be found in the prior art, and must not be based on the applicant's disclosure. Finally, the prior art reference (or references when combined) must teach or suggest all claim limitations. *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991); *In re Dance*, 160 F.3d 1339 (Fed. Cir. 1998); M.P.E.P. 2143.

Prior to analyzing of the cited references, Applicants would like to note that the Examiner

erroneously interpreted the invention of Claim 3 as being drawn to a process for synthesizing a nucleic acid of a known sequence. The term "*sequencing*" is well-known in the art and defined as *the act or process of determining the sequence of proteins or nucleic acids*. See the attached pages from Oxford Dictionary of Biochemistry and Molecular Biology.

Torrence teaches modified 2,5-A ***oligonucleotides*** having the molecular formula:



wherein m is 0, 1, 2, 3 or 4;

Y is always H except on the terminal phosphate where Y may be H, adenosine, or a C_{1-20} primary or secondary alcohol;

n is integer from 1 to 15; and

Z is H or a C_{1-50} hydrocarbon or substituted hydrocarbon bonded to the N of the morpholino ring through one of its carbon atoms. Col. 3, line 1 through Col. 5, line 60; emphasis added.

Torrence teaches that morpholino-modified 2,5-A ***oligomers*** are characterized by having biological activity potentiated beyond that of unmodified 2,5-A oligomers and by being substantially more resistant to degradation than 2,5-A ***oligomers***. Torrence teaches that morpholino-modified 2,5-A ***oligomers*** can act in vitro or in vivo (a) to circumvent interferon by mimicing and/or displacing it in the above-described system, (b) as an antagonist to block the action of interferon produced by the cells. Torrence teaches that morpholino-modified 2,5-A ***oligomers*** can be used for fine tuning in antitumoral chemotherapy and to avoid

interferon-induced auto-immune diseases such as systemic lupus erythematosus, and "auto-immune deficiency syndrome" as well as (c) as an investigative tool for the biological mechanisms of 2,5-A oligomers. Col. 3, lines 23-36.

Torrence teaches the preparation of morpholino-modified 2,5-A ***oligonucleotides*** by chemical modification of p5'A2'(p5'A2')$_n$p5'A by a periodate oxidation/Schiff base formation/borohydride reduction cycle which gave a series of 2-5A analogues in which the ribose of the 2'-terminal nucleotide was transformed to an N-substituted morpholine (azahexapyranose). Col. 5, lines 61-66; Col. 8, line 47 through Col. 9, line 7.

Primarily dealing with morpholino-modified 2,5-A ***oligomers***, Torrence only mentions that "[f]or pilot studies on the derivatization of 2-5A and related oligonucleotides by the periodate oxidation/Schiff base formation/borohydride reduction sequence, adenosine and ATP were chosen as model substrates, and hexylamine were used as the amine Schiff base formation. Potential complicating side reactions such as β-elimination of the phosphate residue or decomposition of the resultant 3-azahexopyranose ring were not realized since excellent yields of 7 and 8 were obtained from adenosine or ATP when the pH of the medium was controlled carefully at 8.6 after the hexylamine conjugation and at 6.5 after the sodium cyanoborohydride reduction." Col. 11, lines 15-27.

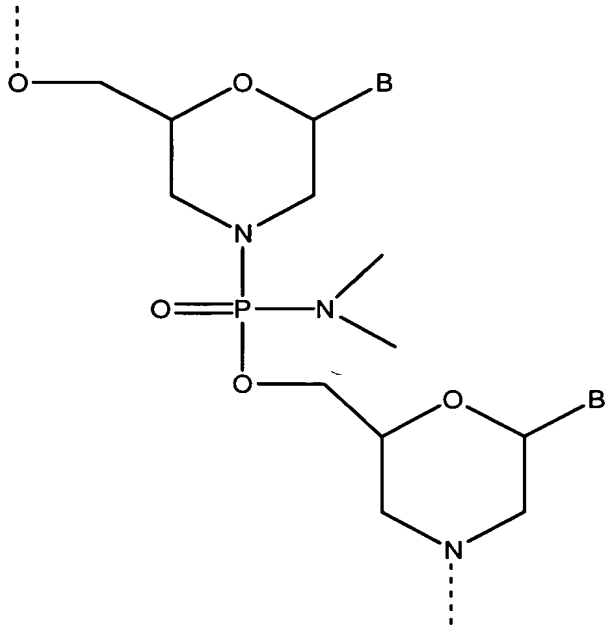
Nowhere does Torrence teach or suggest the presently claimed uses of morpholino-***mononucleotide*** of formula (I) as defined by Claims 1-11 and 18-33, the structures of morpholino-***mononucleotides*** of Claims 12-15 or the process of Claim 16.

Applicants note that Torrence has been already cited in the International Search Report and considered during the International Preliminary Examination of the related

PCT/FR00/00427 application. The International Preliminary Examination Report, a copy of which attached herewith, finds the present invention be patentable over this reference.

The cited Iversen and Meyer references fail to cure the deficiencies in Torrence. As to Meyer, this reference does not even mention morpholinonucleotides. As to Iversen, this reference is limited to antisense oligonucleotides useful for treating a disease state characterized by p53 induction, such as proliferative cell disorders, e.g. cancer, or a hypoxic state induced by an ischemic attack, such as stroke, are described. Iversen teaches the antisense agents which are preferably of the class known as "steric blocker" type oligonucleotides, including morpholino oligonucleotides, peptide nucleic acids, 2'-O-allyl or 2'-O-alkyl modified oligonucleotides, or N3'→P5' phosphoramidate oligonucleotides. Abstract.

In fact, Iversen teaches away from the present invention because Iversen discloses a "morpholino" oligonucleotide composed of morpholino subunit structures of the form:



where (i) the structures are linked together by phosphorous-containing linkages, one to three atoms long, joining the morpholino nitrogen of one subunit to the 5' exocyclic carbon of an adjacent subunit, and (ii) B is a purine or pyrimidine base-pairing moiety effective to bind, by base-specific hydrogen bonding, to a base in a polynucleotide. Col. 4, lines 27-35.

The present invention is directed to morpholino-nucleotides of formula (I) which are not capable to form a bond between the morpholino nitrogen of one subunit and the 5' exocyclic carbon of an adjacent subunit because of the presence of R^2 in their structure, and, thus, these compounds are actually used as chain terminators. See, for example, Specification at page 8, lines 12-18.

Accordingly, Applicants respectfully submit that there would be no motivation for the skilled artisan to modify or combine Torrence, Iversen and Meyer teachings in order to use a morpholino-nucleotide of formula (I) either in process for manufacturing a 3'-labelled nucleic acid fragment, which process comprises the enzymatic incorporation of a nucleotide derivative having as precursor a compound of formula (I) (Claim 1); or in process for modifying a nucleic acid fragment by enzymatic incorporation at the 3' end of a modified morpholino nucleotide having as precursor a compound corresponding to the formula (I) (Claim 2); or in process for sequencing a nucleic acid by the technique of enzymatic polymerization of the sequence complementary to this nucleic acid using chain terminators, in which at least one of the chain terminators has as precursor a compound corresponding to the formula (I) (Claim 3) or obtain the structures of morpholino-nucleotides of Claims 12-15 using the process of Claim 16. Nor would the skilled artisan have a reasonable expectation

that such a combination will produce the claimed uses of a morpholino-nucleotide of formula (I), structures of Claims 12-15 or process of Claim 16. Finally, the combination of Torrence, Iversen and Meyer cannot be used to arrive at the claimed uses, structures and process. Such uses, structures and process are neither disclosed nor suggested by these references, alone or in combination.

Therefore, in light of the above remarks, Applicants respectfully request that the 35 U.S.C. § 103(a) rejection be withdrawn.

Claim 17

Cancellation of Claim 17 renders this rejection moot.

Conclusions:

For the reasons set forth above, Applicants submit that the claims of this application are patentable. Reconsideration and withdrawal of the Examiner's rejections are hereby requested. Early allowance of the claims of this application is earnestly solicited.

Respectfully submitted,

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